Attorney's Docket No. US-109

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:	
HIRANO et al.	Art Unit: 1652
Application No.: 10/784,986	Examiner: Gebreyesus, Kagnew H.
Filing Date: February 25, 2004	Attorney Ref. No.: US-109
For: NOVEL LYSINE DECARBOXYLASE GENE AND METHOD FOR PRODUCING L-LYSINE	Confirmation No.: 1388

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Commissioner for Patents
Alexandria, Virginia 22313

Sir:

In response to the Final Office Action dated February 16, 2006, the response period being extended by a one-month extension of time and a Notice of Appeal filed herewith, to June 16, 2006, Applicants request a Pre-Appeal Brief Review in accordance with the guidelines set forth in the July 12, 2005 Official Gazette Notice. Reconsideration of this application by a three Examiner panel is requested in view of the following remarks which identify the errors in facts, and the omission of essential elements required to establish a *prima facie* rejection.

Summary of Final Office Action and Status of Case

In the February 16, 2006 Final Office Action, claims 7-9, 12, and 13 were rejected under 35 U.S.C. §103 over U.S. Patent No. 5,827,698 to Kikuchi et al. ("Kikuchi") and WO2000/61723 to Gunji et al. ("Gunji"). Claim 7 had been previously cancelled, so it is assumed the rejected claims are 8, 9, 12, and 13. Kikuchi is applied for an alleged teaching of a method of producing an increased level of L-lysine by disrupting the L-lysine decarboxylase genes (cadA and ldc) in *E. coli* using a plurality of methods including substituting a normal polynucleotide in the genome of the bacterium by a modified polynucleotide or disrupting or

polynucleotides using homologous recombination. Gunji is applied for the alleged teaching of a method of making L-lysine using a methanol assimilating bacterium transformed with a mutant LysE gene. The Examiner alleges that it would have been obvious to use Kikuchi's method of disrupting the *E. coli* lysine decarboxylase gene to produce higher levels of L-lysine to disrupt the same lysine decarboxylase in *Methylophilus* of Gunji.

The claims currently pending in this application are claims 1-4, 6, 8-9, and 11-13. Claims 1-4, 6, and 11 have been indicated as allowable. Claims 8, 9, 12, and 13 are rejected. Claim 1 is the only independent claim.

Summary of Claimed Invention

The claimed invention is directed to a novel lysine decarboxylase gene and the encoded protein, which has been isolated from a *Methylophilus* bacterium. The gene and the protein are the subject of claims 1-4, 6, and 11, which have been indicated as allowable. A *Methylophilus* bacterium which produces L-lysine by inactivation of the novel lysine decarboxylase gene, and the method for producing L-lysine using this bacterium is the subject of the rejected claims 8, 9, 12, and 13. The lysine decarboxylase gene has been isolated from *Escherichia coli,* but is only 51% homologous with the lysine decarboxylase isolated by the inventors from a *Methylophilus* bacterium.

Factual Errors Requiring Review

There are several errors in the application of 35 U.S.C. §103 to claims 8, 9, 12, and 13. First, the Examiner has failed to address the issue that Gunji is in Japanese, and it does not appear a translation was obtained. As pointed out on page 9 of Applicants' response filed November 14, 2005, it is unclear how the Examiner is reading and applying Gunji, since this publication contains only a short English abstract. Despite Applicants' request for clarification of this point, the Examiner has merely re-applied Gunji, but withdrawn the US publication which was jointly cited in the First Office Action of March 31, 2005 (and which the Examiner incorrectly believed to be an equivalent to Gunji). As Gunji is assigned to the same company as the instant application, Applicants have provided their description of the teachings. However, it is still unclear how the Examiner can apply Gunji when he has not addressed whether he can understand the reference, nor does he point to the specific teachings in the reference on which he is relying, nor does he state that he is relying on Applicant's

characterization. It is asserted that such is clear error, since no *prima facie* case of obviousness can be made when support in the relied upon reference is not pointed to or clarified.

Secondly, on page 2 of the June 1, 2006 Advisory Action, the Examiner asserts that Applicants, in addressing the Final Rejection set forth in the February 16, 2006 Office Action, fail to address the combination of references in the rejection. This statement represents a clear error in the Examiner's interpretation of Applicants' arguments, and therefore, the Examiner misinterpreted and failed to adequately address Applicants' arguments.

On page 7 of Response to the Final Rejection filed May 16, 2006, Applicants address why the teaching of the *E. coli* lysine decarboxylase gene of Kikuchi et al. would not lead one of ordinary skill in the art to determine the gene sequence of the inventive lysine decarboxylase (now allowable in the form of claims 1-4 and 6). Certainly, if it is not obvious to one of ordinary skill in the art to determine the gene sequence of the claimed lysine decarboxylase, then it is unclear how one of ordinary skill in the art would be able to isolate a bacterium containing the inventive lysine decarboxylase in disrupted form, and a method of making L-lysine using said bacterium. There is no teaching in either reference that a lysine decarboxylase gene even exists in *Methylophilus,* nor that such a gene would be 51% homologous, nor that it would act the same as the *E.coli* gene when disrupted. Hence there is no motivation to combine these references.

Furthermore, contrary to the Examiner's assertion, the second full paragraph on page 7 of our response of May 16, 2006 clearly addresses the combination of the two references, since this paragraph explicitly addresses why Gunji fails to make up for the deficiencies of Kikuchi. Specifically, Applicants state that one of skill in the art would not be motivated to combine the teachings of these references since there is no indication that the gene of Kikuchi, which is very dissimilar as compared to the claimed (and allowed) gene, would even exist or function in the *Methylophilus* as does the DNA of allowed claims 3 and 4.

More specifically, Kikuchi et al. describe a lysine decarboxylase gene which is only 51% homologous with the nucleotide sequence of SEQ ID NO:3. The sequences are very dissimilar and hence one of ordinary skill in the art would not be expected to arrive at the inventive DNA sequence, the *Methylophilus* bacterium, and/or the disrupted gene resulting in suppression of lysine decarboxylase activity, without undue experimentation. As claims 8

and 12 recite that the DNA of claims 3 and 4, respectively, is disrupted, clearly the skilled art worker would not have motivation to arrive at the DNA sequence, disrupt it, and use it in a *Methylophilus* bacterium to produce L-lysine. Deducing the DNA of claims 3 and 4 from the disclosure of Kikuchi is clearly not expected, and in fact, there is clearly no motivation to arrive at the inventive DNA of claims 3 and 4 based upon the dissimilar DNA sequences, and therefore, there is no motivation for arriving at the bacterium or method of claims 8 and 12.

Gunji fails to make up for the deficiencies of Kikuchi with respect to the subject matters of the pending claims, since Gunji only describes the use of *Methylophilus* bacteria for producing L-amino acids, and discloses nothing of disrupting any gene for any purpose, and certainly not for the purpose of suppressing lysine decarboxylase activity. Furthermore, Gunji et al. does not mention the lysine decarboxylase gene of any sequence. Since there is no mention of a lysine decarboxylase gene, there is certainly no motivation to combine this disclosure with the disclosure of Kikuchi, which only teaches a lysine decarboxylase which is only 51% homologous to the novel lysine decarboxylase of the present invention. Furthermore, one of skill in the art would not be motivated to combine the teachings of these references since there is no indication that the gene of Kikuchi, which is very dissimilar as compared to the claimed gene, would function in the *Methylophilus* as does the DNA of claims 3 and 4.

For at least the foregoing reasons, Applicant respectfully submits that the subject matters of Claims 8, 9, 12, and 13, each taken as a whole, would not have been obvious to one of ordinary skill in the art at the time of Applicant's invention, are therefore not unpatentable under 35 U.S.C. § 103(a), and therefore respectfully requests withdrawal of the rejection thereof under 35 U.S.C. § 103(a).

Accordingly, the Final Office Action includes a clear error in failing to carry the PTO's burden in providing sufficient evidence or reasoning of obviousness, and for failing to provide citations for support in the teachings of Gunji.

Conclusion

In the interest of brevity, Applicant does not provide all arguments that would support an appeal for each of the pending and rejected claims. However, it is respectfully submitted that this case is in immediate and clear form for allowance based on the clear errors and omissions cited above. Accordingly, an early indication via a Notice of Allowability that all

claims are allowable is respectfully requested. Should any questions arise in connection with this application or should the Examiner believe that a telephone conference with the undersigned would be helpful in resolving any remaining issues pertaining to this application, the undersigned respectfully requests that he be contacted at the number indicated below.

Respectfully submitted,

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